Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Rejection of Claims 90-129 under 35 U.S.C. § 112, First Paragraph

Claims 90-129 stand rejected under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Office Action states:

> With the exception of SEQ ID NO's: 1 and 2 of the instant application, the skilled artisan cannot envision the detailed chemical structure of the encompassed amino acids and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

This rejection is respectfully traversed.

Applicants submit that the information disclosed in the specification combined with the knowledge of the art provides sufficient guidance to one skilled in the art to isolate aminopeptidases from other strains of *Aspergillus*. The description as a whole is sufficient to evidence possession of the claimed aminopeptidases because Applicants disclose that the aminopeptidases have the physicochemical properties of (i) a pH optimum in the range of from about pH 7.27 to about pH 10.95 determined at ambient temperature in the presence of Ala-para-nitroanilide; (ii) a temperature stability of 90% or more, relative to initial activity, at pH 7.5 determined after incubation for 20 minutes at 60°C in the absence of substrate; and (iii) an ability to hydrolyze a substrate containing Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Phe, Pro, Ser, Thr, Trp, Tyr, or Val at its N-terminus. Applicants also describe in the Examples of the specification methods for isolating and characterizing the aminopeptidases. Moreover, Applicants provide a detailed description of how to identify and isolate genes encoding such aminopeptidases. Thus, there is sufficient written description in the specification to inform the skilled artisan that Applicants were in possession of the claimed aminopeptidases at the time the application was filed.

For the foregoing reasons, Applicants submit that the rejections under 35 U.S.C. § 112, first paragraph, have been overcome and respectfully request reconsideration and withdrawal of the rejections.

II. The Rejection of Claims 90-129 under 35 U.S.C. § 112, First Paragraph

Claims 90-129 stand rejected under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Specifically, the Office Action states:

> The specifications guidance does not enable a skilled artisan to obtain the appropriate peptides. The specification does not provide a specific probe, hybridization conditions or a library from which an aminopeptidase with the claimed characteristics may be isolated. The artisan, based on the limited guidance is not reasonably assured of reproducibly and reliably obtaining the claimed aminopeptidases as directed. Further, the artisan would be forced, after obtaining a candidate agent to perform undue experimentation to determine the full open reading frame, express the protein and determine the peptides biological properties as well as its functional characteristics. The specification is required to be fully enabled at the time of the invention. However, applicants do not provide evidence of reduction to practice for any other aminopeptidase other than that of SEQ ID NO:2. The specification merely invites the artisan to discover other related sequences. The single species does not support the genus claim.

This rejection is respectfully traversed.

Applicants' contribution to the art is the discovery of a polypeptide having aminopeptidase activity, wherein the polypeptide has the ability to hydrolyze a proteinaceous substrate containing Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Phe, Pro, Ser, Thr, Trp, Tyr, or Val at its N-terminus. Moreover, Applicants have provided detailed instructions on how to obtain such polypeptides and nucleic acid sequences encoding such polypeptides. Applicants' specification provides adequate guidance for finding such aminopeptidases encoded by a nucleic acid as detailed in Examples 1-8 of the specification. Moreover, Applicants detail on page 3, line 37, to page 6, line 10, of the specification, how to further isolate and characterize such aminopeptidases. Furthermore, hybridization conditions and protocols are defined on page 5, line 18, to page 6, line 18, of the specification. On the basis of

Applicants' disclosure, one skilled in the art would know how to identify and isolate such aminopeptidases. Applicants, therefore, submit that the information disclosed in the specification enables one skilled in the art to isolate the claimed aminopeptidases.

The Office Action states that "[t]he specification does not teach any peptide which corresponds to the recited % identity or fragment thereof, which retains aminopeptidase activity." As noted above, Applicants have provided detailed methods for isolating an aminopeptidase and determining whether it falls within the scope of protection sought by Applicants. It is well within the skill of the art to practice the invention using Applicants' disclosure.

The Office Action also states that "[a]s to claims 90-129 with respect to hybridizing and complementary strands, the skilled artisan is well aware that the complementary strand, i.e., the non-coding strand, are unrelated to the coding sequence. Thus the applicant is not enabled for the use of a vector and host cell expressing the complementary strand or hybridizing sequences which encodes an aminopeptidase because the protein encoded by the opposite strand is unrelated structurally and functionally to aminopeptidase sequences." Applicants respectfully note that the claims do not recite that the complementary or hybridizing strand encodes an aminopeptidase, but rather a polypeptide having aminopeptidase activity is encoded by a nucleic acid sequence which hybridizes under medium stringency conditions with the nucleic acid sequence of nucleotides 46 to 1488 of SEQ ID NO:1, or its complementary strand. One skilled in the art would readily understand that a nucleic acid sequence encoding a protein necessarily must be denatured into its separate strands to undergo hybridization. The strands alone do not encode a polypeptide.

The facts in the present case are similar to those in *In re Wands*, 8 U.S.P.Q.2d at 1406-07. The claimed invention in *In re Wands*, *supra* involved methods for the immunoassay of hepatitis B surface antigen (HBsAg) by using high-affinity monoclonal IgM antibodies having specified properties. A hybridoma cell line that secretes IgM antibodies against HBsAg was deposited at a recognized cell depository. The claims, which were not limited to the deposited cell line, were

rejected for lack of enablement. The Federal Circuit reversed the rejection as follows:

> When Wands' data is interpreted in a reasonable manner, analysis ... leads to the conclusion that undue experimentation would not be required to practice the invention. Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.
>
> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen. However, it seems unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened.

In re Wands, 8 U.S.P.Q.2d at 1406-07.

Applicants also respectfully submit requiring applicants to limit the claims to the deposited strain would be contrary to public policy as set forth in *In re Goffe*, 191 U.S.P.Q. 429, 431 (C.C.P.A. 1976):

> For all practical purposes, the board would limit appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently-issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for 'preferred' materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

In the instant case, claims limited to the deposited strain would not adequately protect the inventors. Based on the teachings of the present application, one skilled in the art would attempt to find another aminopeptidase having the properties of the aminopeptidases of the present invention and thereby attempt to circumvent the literal scope of Applicants' patent rights.

For the foregoing reasons, Applicants submit that the rejections under 35 U.S.C. § 112, first paragraph, have been overcome and respectfully request reconsideration and withdrawal of the rejections.

III. The Rejection of Claims 110 and 129 under 35 U.S.C. § 112, First Paragraph

Claims 110 and 129 stand rejected under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Specifically, the Office Action requested a declaration that *E. coli* NRRL B-21677 is readily available.

As requested, Applicants enclose a Statement under 37 C.F.R. § 1.808 that the strain was deposited under the Budapest Treaty and all restrictions will be removed upon the granting of the U.S. patent. Applicants therefore submit that this rejection has been overcome.

IV. The Rejection of Claims 90-129 under 35 U.S.C. § 112, First Paragraph

Claims 90-129 stand rejected under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Office Action states::

> Claims 90-129 recite the new limitation, "wherein the polypeptide having aminopeptidase activity sequentially removes one amino acid residue at a time from the N-terminus of the peptide, polypeptide, or protein."

This rejection is respectfully traversed.

Applicants respectfully assert that one skilled in the art would clearly and readily understand that an aminopeptidase sequentially removes one amino acid residue at a time from the N-terminus of a peptide, polypeptide, or protein, as long as the amino acid following the cleaved amino acid is a substrate for the aminopeptidase. In the instant invention, the aminopeptidase has a broad specificity toward a number of amino acids. Moreover, Applicants on page 4, lines 21-25, of the

specification, state:

> Defined in a general manner, the aminopeptidase activity is capable of cleaving the amino acid X from the N-terminus of a peptide, polypeptide, or protein, wherein X may represent any amino acid residue selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val, but at least Leu, Glu, Gly, Ala, and/or Pro.

Applicants contend that this definition clearly indicates one amino acid at a time is cleaved from a peptide, polypeptide, or protein.

For the foregoing reason, Applicants submit that the rejections under 35 U.S.C. § 112, first paragraph, have been overcome and respectfully request reconsideration and withdrawal of the rejections.

V. The Rejection of Claims 90-129 under 35 U.S.C. § 112, Second Paragraph

Claims 90-129 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to specify the conditions of medium stringency.

Applicants have cancelled claims 90-129 but have included the specific conditions of medium and high stringency in the new claims.

For the foregoing reason, Applicants submit that the new claims overcome the rejections under 35 U.S.C. § 112, second paragraph. Applicants respectfully request reconsideration and withdrawal of the rejection.

VI. The Rejection of Claims 90-129 under 35 U.S.C. § 102

Claims 90-129 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Kauppinen *et al.* (WO 96/28542). The Office Action states:

> Kauppinen et al. disclose an *Aspergillus oryzae* aminopeptidase which cleaves peptides. The proteins of instant claims share a single amino acid fragment with the WO 96/28542 aminopeptidase.

This rejection is respectfully traversed.

Kauppinen *et al.* disclose an *Aspergillus oryzae* aminopeptidase having a molecular weight of 35 kDa.

However, Kauppinen *et al.* do not disclose the aminopeptidases claimed herein. Applicants submit herewith a copy of the Declaration of Dr. Alexander Blinkovsky filed on June 3, 1999, in response to the Office Action dated December 8,

1998. The Declaration provides that the amino acid sequence of the Kauppinen aminopeptidase is 13.5% identical to the aminopeptidase of SEQ ID NO. 2. This low degree of identity between the amino acid sequences of the two aminopeptidases indicates that the corresponding genes, and subsequences of the genes which encode polypeptides having aminopeptidase activity, would not hybridize under medium stringency conditions as defined by prehybridization and hybridization at 42°C in 5X SSPE, 0.3% SDS, 200 μg/ml sheared and denatured salmon sperm DNA, and 35% formamide, following standard Southern blotting procedures. A subsequence is a nucleic acid sequence where one or more nucleotides have been deleted from the 5' end and/or 3' end of the nucleic acid sequence, wherein the subsequence encodes a polypeptide fragment which has aminopeptidase activity. The polypeptide fragment preferably contains at least 330 amino acid residues. (See page 4, lines 30-31, and page 9, lines 25-26, of the specification).

For the foregoing reasons, Applicants submit that this rejection under 35 U.S.C. § 102 has been overcome. Applicants respectfully request reconsideration and withdrawal of the rejection.

VII. The Rejection of Claims 90-129 under 35 U.S.C. § 102

Claims 90-129 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Nishizawa *et al.* (*Journal of Biological Chemistry* 269: 13651-13655, 1994). The Office Action states:

> Nishizawa teach a *S. cerevisiae* aminopeptidase which hybridizes with SEQ ID NO:1, its complementary strand and a subsequence of SEQ ID NO:1 which retains aminopeptidase activity, is a fragment of a, b or c which retains aminopeptidase activity and which inherently has the physicochemical properties of e, see in particular attached alignment of amino acids.

This rejection is respectfully traversed.

Nishizawa *et al.* disclose a *Saccharomyces cerevisiae* aminopeptidase Y which is a vacuolar enzyme consisting of 537 amino acids.

However, Nishizawa *et al.* do not disclose the aminopeptidases claimed herein. The Office Action indicates that a sequence comparison shows that the deduced amino acid sequence of the *Saccharomyces cerevisiae* aminopeptidase Y is

31.3% identical to the deduced amino acid sequence of the aminopeptidase of the instant invention. This low degree of identity between the amino acid sequences of the two aminopeptidases indicates that the corresponding genes, and subsequences of the genes which encode polypeptides having aminopeptidase activity, would not hybridize under medium stringency conditions as defined by prehybridization and hybridization at 42°C in 5X SSPE, 0.3% SDS, 200 μg/ml sheared and denatured salmon sperm DNA, and 35% formamide, following standard Southern blotting procedures.

For the foregoing reasons, Applicants submit that this rejection under 35 U.S.C. § 102 has been overcome. Applicants respectfully request reconsideration and withdrawal of the rejection.

VIII. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: November 21, 2000

Robert L. Starnes, Reg. No. 41,324
Novozymes Biotech, Inc.
1445 Drew Avenue
Davis, CA 95616-4880
(530) 757-8100